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Experimental and Clinical Studies on Balloon Laserthermia Using Nd:YAG Laser for Uterine Endometrial Cancer

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Background and Objective: **No conservative therapy for endometrial cancer exists. We therefore evaluated the new balloon laserthermia for such cases.**
Study Design/Material and Methods: **Experimental and clinical study. We examined experimentally porcine kidney and stomach, human resected uterus and clinically on 12 patients with endometrial cancer and two patients with hyperplasia.**
Results: **Temperatures were safely kept at the balloon surface. Laser irradiation shoud be performed for at least 10–15 min, 65–70°C to produce a suitable degeneration, experimentally. Clinically, necrosis and degeneration to a depth of 4–6 mm was histologically observed. Eight patients with carcinoma and hyperplasia for which laserthermia was effective showed that the surface of cancer was smooth and the depth of invasion was in most cases up to 1/4 of muscle layer.**
Conclusion: **Balloon laserthermia may be effective in early endometrial cancer or precancerous lesions. Its clinical usefulness should be investigated further.** © 1996 Wiley-Liss, Inc.

Key words: Nd:YAG laser balloonthermia, endometrial cancer

INTRODUCTION

Since the uterus is a luminal organ, balloon laserthermia can be used to treat endometrial carcinoma. Balloon laserthermia has the potential to produce good results, especially in patients with early cancer and precancerous lesions of the endometrium. Thanks to the development of cytology and hysteroscopy, endometrial cancer is more frequently detected at an early stage, and hysteroscopy has made it possible to correctly determine the extent of lesions and to detect any residual tumor after resection.

We have recently developed a new type of balloon laserthermia system and have used it in combination with a YAG laser feedback system in laboratory and clinical studies.

MATERIALS AND METHODS

Balloon Laserthermia System

The balloon laserthermia system (Fig. 1) that we designed consisted of a ceramic probe that emitted a diffuse laser beam and was covered by a double silicone membrane plus a thermal sensor mounted on the central part of the surface of the probe between the two silicone membranes. To perform laserthermia, the balloon laserthermia system was connected to a YAG laser feedback system [1] (SLT Japan Co., Tokyo, Japan), and air was introduced into the balloon. The volume of air introduced was 11 ml for the balloon with a long diameter of 3 cm and 20 ml for the balloon with a long diameter of 5 cm, and the internal pressure was 0.8 kg/cm^3.

Temperature at Different Sites in the Balloon System and Thermal Distribution in the Uterus

Porcine kidneys were used for determination of the temperature at different sites in the balloon

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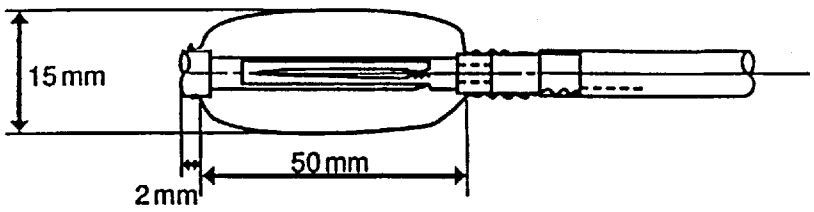


Fig. 1. Laser balloon.

laserthermia system. After anesthesia, the kidney was exposed and a small incision was made in its surface. The balloon system with 3-cm balloon was inserted and then filled with air. As shown in Figure 2, the temperature was measured at the probe base (Tc, Ts), the probe tip (Tp), and the balloon surface (Tm) via the mounted sensor. In addition, the tissue temperature at a site 5 mm deep from the balloon surface (Td) was also measured by inserting a needle sensor.

The intrauterine thermal distribution was determined by measuring the temperatures at the balloon surface, that in the uterine tissue at a site 7 mm deep from the balloon surface, and that in the uterine tissue beneath the serosa, using organs immediately after resection from patients with cervical carcinoma in situ (n = 2), cervical microinvasive carcinoma (n = 1), and uterine myoma with adenomyosis (n = 1). Uteri with a cavity of 6–9 cm in length were selected and were placed in an incubator during the measurement of temperature.

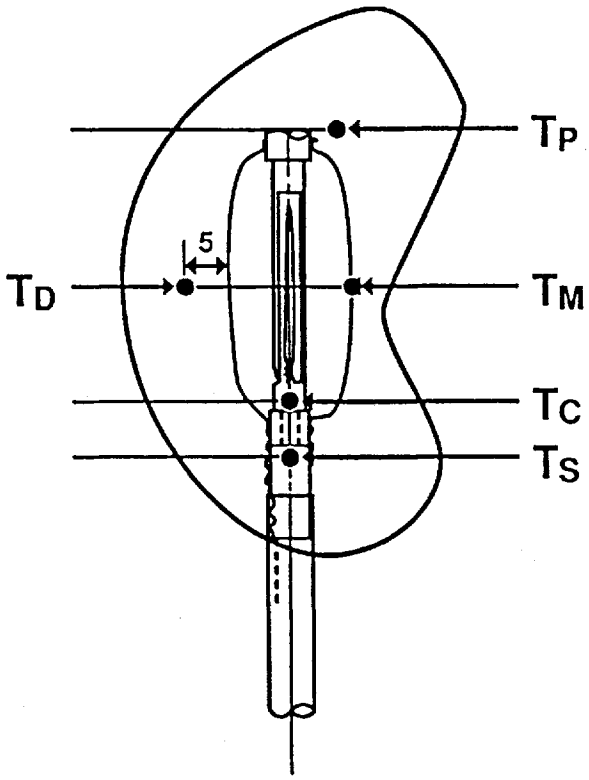


Fig. 2. Temperatures at different sites in the balloon laser system used for the porcine kidney study.

Histological Changes After Laserthermia of Porcine Stomach

In two anesthetized pigs, the stomach was converted into a double-lumen organ. A balloon laserthermia system (5 cm balloon) was inserted into each of the lumens and irradiation was performed for 10 min at 55°C and 70°C. The stomach was resected immediately after irradiation in one pig and after 2 weeks in the other pig. Histological investigation was performed at the site treated with laserthermia using hematoxylin-eosin (H&E) staining and silver staining.

Histological Investigation of the Effect on Human Endometrial Cancer and Endometrial Hyperplasia

The histological changes after laserthermia were investigated in 14 patients with endometrial cancer (stage Ia in 4, stage Ib in 5, and stage IIb in 3) and two patients with endometrial hyperplasia. Laserthermia was performed just before hysterectomy using a 3-cm balloon for patients with a uterine cavity of 5–6 cm in length and a 5-cm balloon for patients with a uterine cavity of 7–9 cm in length. The temperature and duration of laserthermia was 60–70°C and 8–10 min, respectively. The resected uteri were cut into large segments and the sectioned specimen were subjected to H&E staining and silver staining. The depth of

TABLE 1. Temperature at Different Sites in the Balloon Laser System

Condition			Degree		
1. Power	—	20 W	Tc	—	85°C
Degree	—	85°C	Tp	—	75°C
Time	—	10 min	Ts	—	45°C
Balloon vol	—	10 cc	Tm	—	125°C
Total energy	—	5620 J	Td	—	70°C
2. Power	—	20 W	Tc	—	75°C
Degree	—	75°C	Tp	—	59°C (L=35)
Time	—	10 min	Ts	—	38°C (L=28)
Balloon vol	—	10 cc	Tm	—	120°C (L=40)
Total energy	—	9016 J	Td	—	47°C (L=35)
3. Power	—	20 W	Tc	—	65°C
Degree	—	65°C	Tp	—	55°C
Time	—	10 min	Ts	—	36°C
Balloon vol	—	10 cc	Tm	—	90°C
Total energy	—	3338 J	Td	—	59°C
4. Power	—	20 W	Tc	—	65°C
Degree	—	65°C	Tp	—	57°C
Time	—	10 min	Ts	—	47°C
Balloon vol	—	10 cc	Tm	—	115°C
Total energy	—	3418 J	Td	—	53°C
5. Power	—	20 W	Tc	—	75°C
Degree	—	75°C	Tp	—	87°C
Time	—	10 min	Ts	—	36°C
Balloon vol	—	10 cc	Tm	—	110°C
Total energy	—	7904 J	Td	—	60°C

invasion of endometrial carcinoma was classified by dividing the muscle layer into four sections of equal depth. Depth of (1) shows invasion of up to 1/4, (2) up to 1/2, (3) up to 3/4, and (4) over 3/4 of muscle layer. This clinical study was performed after being approved by the ethics committee of Osaka Medical College (approval no. 18).

RESULTS

Temperature at Different Sites in the Balloon Laser System

As shown in Table 1, when the laser was set at a power of 20 W and an operating temperature of 85°C at the base (Tc) (experiment 1), the temperature was 75°C at Tp, 125°C at Tm, and 110°C at Td. In experiments 2–5 using other operating conditions, the temperatures measured at Tp, Tm, and Td varied similarly, showing small differences.

The results of this study indicated that the energy in the balloon increased rapidly until it became stable and that the highest temperature was produced at Tm. It was therefore concluded that the present balloon laserthermia system can be operated safely by monitoring the temperature at Tm.

Uterine Thermal Distribution During Balloon Laserthermia

Balloon laserthermia was performed on the resected uteri, using a balloon with a long diameter of 5 cm (Table 2). The temperature on the inner surface of the balloon was defined as the operating temperature. In experiments 1, 2, and 3, laser irradiation was performed for 5, 7, and 9 min at a power of 20 W and an operating temperature of 65°C. The tissue temperature at a site 7 mm from the inner surface of the balloon was, respectively, 43, 44, and 46°C. In experiment 4, laser irradiation was performed for 9 min at a power of 20 W and 75°C, and the temperature measured at the same site was 47°C. The temperature of the uterine surface was only slightly increased (38–40°C) at any of the operating temperatures, and thus the lack of effect on the surrounding organs was confirmed.

For the treatment of early endometrial cancer with laserthermia, the tissue temperature should be raised to at least 45–47°C in order to produce histological changes at a site deep enough to cover the leading edge of an invasive early cancer (5–7 mm). Therefore, the results of this study suggested that laser irradiation should be performed for at least 10–15 min at a balloon temperature of 65–75°C to produce a suitable increase in the tissue temperature.

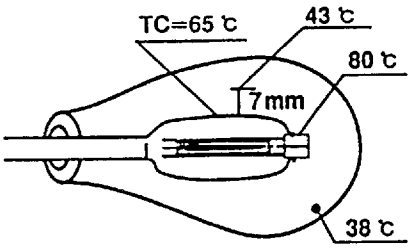
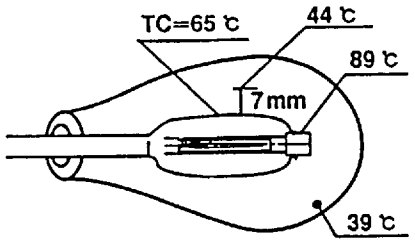
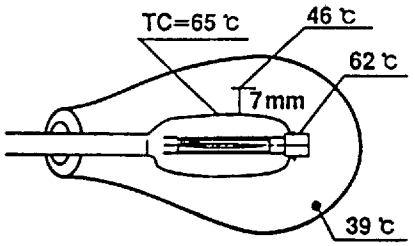
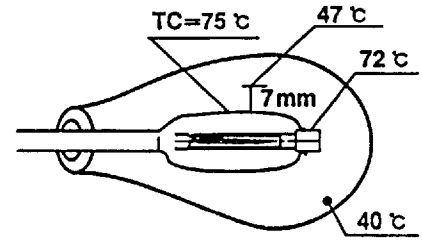
Histological Changes After Laserthermia of Porcine Stomach

After laserthermia for 10 min at 55°C, the treated stomach was immediately removed and subjected to histological investigation. A very thin layer of coagulation (~20 μm) was observed at the surface of gastric mucosa, consisting largely of erythrocyte debris as well as exfoliated epithelium, interstitial cells, and tissue fragments. The effect of laserthermia was observed to a depth of 20–30 μm beneath this layer, with collapse of the glandular structure as well as ablation and hemorrhage of the glandular epithelium being noted.

In the pig kept alive for 2 weeks after laser irradiation for 10 min at 55°C, no changes of the gastric wall were observed either macroscopically or microscopically.

When the stomach was removed immediately after irradiation for 10 min at 70°C, histological changes were observed from the surface of

TABLE 2. Thermal Distribution in the Balloon Laser System Used for Treating Resected Uteri

Experiment I	Laser temperature : 65°C (T.C) Laser power : 20 W Duration of radiation : 5 min Volume of air in the balloon : 20 cc Balloon pressure : 0.8 kg/cm^2	Uterine size 8 cm x 7 cm 
Experiment II	Laser temperature : 65°C (T.C) Laser power : 20 W Duration of radiation : 9 min Volume of air in the balloon : 11 cc Balloon pressure : 0.8 kg/cm^2	Uterine size 6.5 cm x 4.0 cm 
Experiment III	Laser temperature : 65°C (T.C) Laser power : 20 W Duration of radiation : 12 min Volume of air in the balloon : 16 cc Balloon pressure : 0.8 kg/cm^2	Uterine size 9 cm x 4.5 cm 
Experiment IV	Laser temperature : 75°C (T.C) Laser power : 20 W Duration of radiation : 12 min Volume of air in the balloon : 18 cc Balloon pressure : 0.8 kg/cm^2	Uterine size 8 cm x 6.0 cm 

the mucosa to a depth of ~300–500 μm. There was a layer of coagulation ~100 μm thick with the same composition described above. Beneath the coagulation layer, there was glandular collapse, ablation of the glandular epithelium, cavitation of the glandular epithelial cytoplasm and nuclei, interstitial edema, and numerous capillary thrombi and hemorrhages. In the pig kept alive for 2 weeks after identical laser irradiation, there was mucosal loss over 1/3 of the site treated with laserthermia and granulation tissue was observed around the defect and at its base.

Histological Changes and Outcome of Laserthermia in Human Endometrial Cancer and Hyperplasia

Histological changes were investigated in resected uteri after intrauterine laserthermia (65–70°C and 10–12 min) was performed in patients with endometrial cancer or hyperplasia immediately before surgery. In contrast to the histological changes in the pig stomach, a bloody coagulum 2–3 mm in thickness was formed by hemorrhage at the surface of the uterine cavity where the balloon was in contact (Fig. 3). The coagulum mainly consisted of erythrocytes and exudate plus necrotic fragments of the superficial layer of the endometrium. Degenerated or necrotic glandular tissue and damaged glandular epithelium and interstitial cells were also found in this layer. There was a layer of endometrial degeneration 3–4 mm thick below the coagulum, involving total and partial collapse of the glandular structure, vacuolization of the cytoplasm and nuclei of glandular epithelial cells, hypochromatic changes of endometrial interstitial cells, edematous change of the interstitium, capillary thrombosis, capillary endothelial degeneration, and elongation of the cytoplasm and nuclei of the muscular cells (Fig. 4). There was an intact layer beneath the layer of degeneration that was normal under the light microscope. Its border was poorly defined by H&E staining. There was no damage or degeneration of the glandular epithelial cells, and the elongation of muscular cells as well as capillary thrombosis and interstitial edema were not present in the intact layer.

Electron microscopic findings. Endometrial tissue samples were collected from a site ~6 mm below the surface and embedded in epoxy resin (Epon) according to the standard method. No distinct degeneration was observed in the sampled tissue under the light microscope. In the endometrial glands, electron microscopy revealed the presence of exudate and cell fragments in the glandular cavity. Other electron microscopic findings were the absence of microvilli and degeneration or the loss of organelles such as mitochondria and the Golgi apparatus as well as the absence of a clear border between the cells. There were minor changes in the nuclei. In the muscular cells, electron microscopy revealed the presence of perinuclear halo and the absence of organelles in the perinuclear region, although filaments were still present in the cytoplasm. The nuclear membranes were obscure, suggesting that there had been damage to the nucleus (Figs. 5 and 6).

Fig. 3. Hysterectomied uterus after laserthermia for early endometrial cancer. Coagulum in the whole uterine cavity is seen. The blackened adnexae were hyperemia due to operation, not laserthermia. Original color photo shows red adnexae.

The 14 patients who underwent laserthermia and then hysterectomy were divided into effective and ineffective groups. An effective outcome of treatment was defined as the complete or almost complete disappearance of endometrial cancer or endometrial hyperplasia. In other patients much cancerous tissue was observed.

Balloon laserthermia was effective for endometrial cancer or hyperplasia in seven out of fourteen patients (Table 3), including one with the complete disappearance of adenomatous hyperplasia (ADH). In the other patients of the effective group, there was some remnant of the lesion (~0.3 × 0.7 cm at the largest) unilaterally or bilaterally in the uterine fundus (commonly around the tubal ostium). In the patients with endometrial cancer for which laserthermia was effective, the depth of invasion was (a) in five cases and (b) in one patient (see Table 3).

Balloon laserthermia was ineffective in another seven patients, all of whom had endometrial cancer (Table 4). The tumor was classified as stage II in two patients and stage I in five patients, and its histology was G2 (moderately differentiated) in two patients and G1 in the other patients. The depth of invasion was (b) in three patients, (c) in two, and (d) in one (see Table 4). Insufficient laser irradiation was given to one patient of each group because of technical problems. There were nodular or polypoid elevations or de-

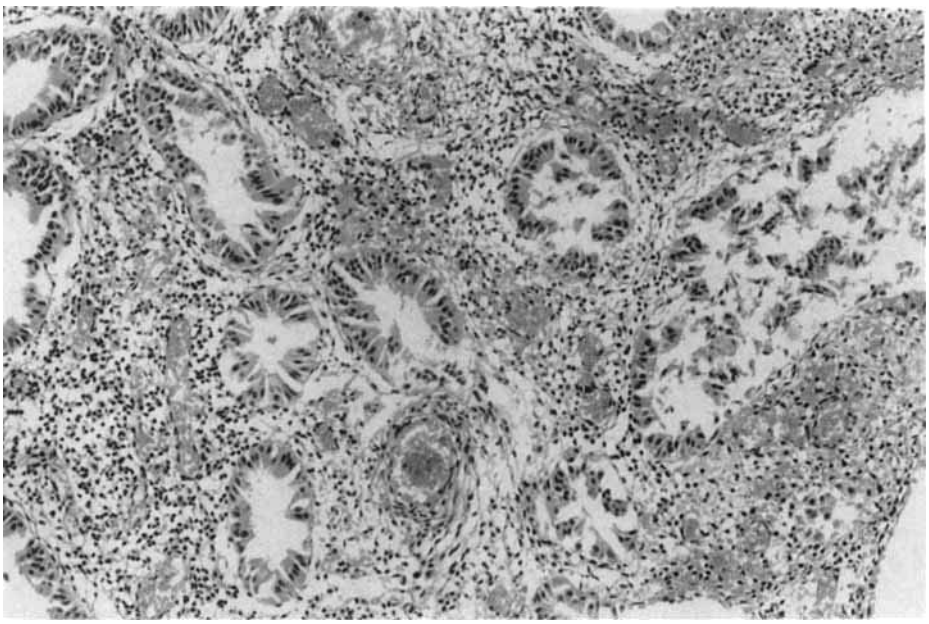


Fig. 4. Histological findings of photo 1 (×100, H&E stain) Degenerating layer 3–4 mm thick below the coagulum consists of damaged glands, degenerated glandular cells and stromal cells, bleeding, and capillary thrombosis.

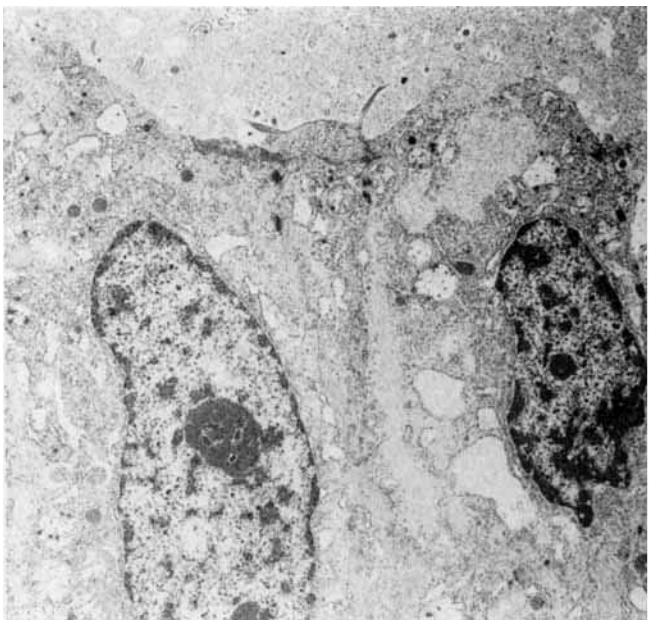


Fig. 5. Electron microscopic findings of endometrial cancer gland, collected from a site below the endometrial surface of a hysterectomied uterus after laserthermia. The absence of microvilli and degeneration or loss of organelles as well as the absence of a clear border between the cells are observed.

Fig. 6. Electron microscopic findings of muscle cells at same site of Figure 5. The presence of perinucleal halo and the absence of organelles in the perinuclear region are observed, although filaments are still present in the cytoplasm.

pressions on the surface of the intrauterine cavity in the ineffective group, and a large remnant of the lesion was found. Relationship between the effectiveness of laserthermia and the differentiation of endometrial cancer was not defined because most cases showed G1.

TABLE 3. Patients With an Effective Outcome of Balloon Laserthermia

Patients with endometrial cancer

		Stage	Histology Infiltration of the muscle layer	Thermia: Balloon size	Thermia: Temperature time	Timing of hysterectomy	Tissue degeneration: Body	Tissue degeneration: Fundus	Remnant lesion: Location	Remnant lesion: Range
1.	K.Y. (38 years old)	IbG1	Diffuse depth a	5 cm	65°C 15 min	Immediately after laser-thermia	Intensive	Intensive	Uterine cornu	0.5 × 1.0 cm
2.	N.M. (53 years old)	IaG1	Diffuse depth a	5 cm	70°C 11 min	Immediately after laser-thermia	Intensive	Intensive	Uterine cornu	0.4 × 0.5 cm
3.	M.T. (54 years old)	IaG1	Diffuse depth a	3 cm	70°C 8 min	Immediately after laser-thermia	Intensive	Intensive	Uterine cornu, uterine body	Minimal
4.	O.C. (45 years old)	IaG1	Multiple polyp depth b	5 cm	68°C 10 min	Immediately after laser-thermia	Intensive	Intensive	Uterine cornu, uterine body	0.3 × 0.5 cm Minimal
5.	I.A. (63 years old)	IIbG1	Diffuse Body: depth a Cervix: depth b	5 cm	60°C 15 min	Immediately after laser-thermia	Intensive	Intensive	Uterine cornu, body, and fundus	0.5 × 0.7 cm Minimal
6.	M.A. (49 years old)	IaG1	Diffuse depth a	5 cm	66°C 12 min	Immediately after laser-thermia	Intensive	Intensive	Uterine fundus	Minimal

Patients with endometrial hyperplasia

		Pretreatment diagnosis Uterine cavity length	Chief lesion	Thermia: Balloon size	Thermia: Temperature time	Timing of Hysterectomy	Tissue degeneration: Body	Tissue degeneration: Fundus	Remnant lesion: Location	Remnant lesion: Range
7.	M.H. (55 years old)	ADH 6.5 cm	Ovarian cyst (LPM)	3 cm	70°C 15 min	Immediately after laser-thermia	Intensive	Intensive	Uterine cornu	Minimal
8.	K.Y. (59 years old)	ADH 6.0 cm	Ovarian cancer	3 cm	50°C 9 min	After 2.5 months	—	—	None	

DISCUSSION

An increasing incidence of endometrial cancer has been reported with the improvement of diagnostic procedures, and early endometrial cancer and precancerous lesions (endometrial hyperplasia) have come to be detected more often in young women. Hysterectomy is used for the radical treatment of endometrial cancer since it is difficult to perform hormone therapy intensively enough to produce an adequate outcome. Radiotherapy is not warranted in young patients due to destruction of the reproductive process.

Electrocautery [2,3], radiofrequency hyperthermia [4], and laser photo vaporization [5] have conventionally been applied for hemostasis or ablation in the treatment of endometrial abnormalities. However, considerable skill is necessary to perform these procedures successfully, and none of the existing approaches achieves complete ablation. Therefore, these methods have not commonly been adopted for the treatment of endometrial cancer. Accordingly, the present study assessed the effect on the uterine cavity of direct laser light and its heating, since this approach seemed to have the potential to provide uterus-preserving therapy for early endometrial cancer.

Previously, relatively low temperature laserthermia was studied for gastric cancer by inserting a laser probe and a thermal sensor into the lesions [6–8]. However, this method was effective only for small localized early lesions, and a high level of skill was necessary to perform it. The balloon laser method was subsequently developed in which the laser fiber is inserted into a balloon

TABLE 4. Patients With an Ineffective Outcome of Balloon Laserthermia

Patients with endometrial cancer									
			Thermia			Tissue degeneration		Remnant lesion	
	Stage	Histology Infiltration of the muscle layer	Balloon size	Temperature time	Timing of Hysterectomy	Body	Fundus	Location	Reasons for an ineffective outcome of laserthermia
9. K.Y. (66 years old)	IIbG2	Overall elevation/ depression depth b	5 cm	55°C 8 min	Immediately after laser-thermia	Moderate	Moderate	Uterine body and fundus	Overall elevation and depression, depth c
10. T.A. (48 years old)	IbG1	Multiple polyp depth b	5 cm	70°C 1 min	Immediately after laser-thermia	Slight	Slight	Entire uterus	Technical problems with the balloon system Insufficient duration of irradiation
11. N.F. (40 years old)	IbG1	Generalized nodularity depth b	5 cm	70°C 10 min	Immediately after laser-thermia	Intensive	Intensive	Uterine cornu, body, and fundus	Generalized nodularity and irregularity
12. S.M. (79 years old)	IIbG1	Extensive tumor mass depth b	5 cm	70°C 13 min	Immediately after laser-thermia	Slight	No degeneration	Entire uterus	Inappropriate posi tioning of the balloon system depth d
13. M.Y. (61 years old)	IbG1	Generalized nodularity depth c	5 cm	70°C 15 min	Immediately after laser-thermia	Intensive	Intensive	Body, and fundus	Generalized nodularity and irregularity depth c
14. S.H. (55 years old)	IbG1	Nodularity depth b	5 cm	70°C 15 min	Immediately after laser-thermia	Intensive	Intensive	Uterine cornu	Nodularity at uterine cornu

filled with 20% Intralipid to disperse the laser beam. This method has been reported to be effective clinically as it allows the elevation of temperatures that can be maintained [9]. However, there was still a risk that the laser fiber inside the balloon might be damaged or melt. We therefore developed the present balloon laser system employing a probe (3 or 5 cm long) to radiate diffused laser light into the balloon.

Laserthermia is performed at both relatively low temperatures (43–45°C) and high temperatures (60–70°C). With the former method, no apparent changes are seen both macroscopically and microscopically immediately after irradiation, but ultrastructural changes are produced. In contrast, the other method produces coagulation of the superficial layer and degeneration in the next layer, which can be observed both macro- and microscopically. Laserthermia is performed at 70–90°C for the treatment of prostatic hypertrophy [10]. The laser can be applied at such a high temperature because the adjacent organ can be cooled simultaneously, and necrosis is achieved by direct laser irradiation at these temperatures.

Our method of balloon laserthermia is performed at a high temperature for the following reasons. Early endometrial cancer invades to a depth of ~5–7 mm beneath the endometrial surface. The border between the endometrium and the muscle layer is not smooth, and the cancer sometimes partly invades the muscle. In addition, an endometrial cancer and its surrounding precancerous tissue commonly form a diffuse lesion even in the case of early cancer.

Thus if laserthermia was performed at a low temperature, heating would penetrate only a few millimeters due to the cooling effect of blood flow. Therefore, despite the surface necrosis, high temperature laserthermia is considered to be necessary to produce degeneration of the deeper tissues. In laserthermia, a cytocidal effect is thought to be produced not only by heat but also by the laser beam itself. Concerning the effect of Nd: YAG laser, we have found that the cellular damages were found to be clearer by heat plus laser than by heat only in our experimental study using cell culture of endometrial cancer (unpub. data).

Our laser balloon made it possible to safely perform laser irradiation of the uterine cavity, to rapidly elevate the balloon temperature to a stable level, and to achieve adequate heating of the deeper tissues. Since the tissue temperature was increased to 46–47°C at a depth of ~7 mm when

balloon laser irradiation was performed at 65–70°C, it appears that effective treatment can theoretically be performed with the present method. Tissue degeneration was observed in the H&E-stained specimens of the resected uterus to a depth of 6–7 mm from the endometrial surface. Electron microscopy also revealed obvious ultrastructural degeneration in the glandular epithelium and muscle cells obtained from a depth of 6 mm. The ultrastructural changes occurring immediately after laserthermia cannot be shown microscopically by current staining techniques, but are demonstrated by microscopy at 1–2 weeks after laserthermia. It was impossible to investigate the time course of degenerative changes in the treated tissues because of ethical restrictions imposed on doctors by our hospital's ethics committee to protect the human rights of our patients. However, this may be possible in the future.

The endometrial cancers that responded effectively to balloon laserthermia were usually stage Ia and had depth (a) invasion. The cancer was usually a diffuse lesion and there was no irregularity of endometrial surface in such patients. However, the cancer remained partially viable in all of these patients and a remnant lesion was present in the fundus commonly around the bilateral tubal ostia. This finding indicates a defect of the balloon laser system that needs to be rectified. In the two ADH patients showing effective treatment by balloon laserthermia, there was a remnant lesion in one case and complete ablation in the other. In the patients with endometrial cancer who did not respond to balloon laserthermia, tumor invasion was more extensive and the surface of the lesion was quite irregular forming a nodular or polypoid mass. Our findings suggest that balloon laserthermia is ineffective for patients with endometrial cancer invading 1/4 or more of the muscle layer.

Balloon laserthermia was also performed in three patients (Cystic Glandular Hyperplasia in 1, ADH in 1, and Atypical Hyperplasia 1) using hysteroscopy and cytology and follow-up is still ongoing (6–10 months at present). There were no remnant lesions and endometrial atrophy was noted in all of the patients (unpub. obs.). Both the results of the present study and these findings suggest that laserthermia using our balloon laser system may be very useful for the treatment of precancerous uterine lesions.

Based on these findings, the clinical usefulness of the present balloon laserthermia system should be assessed further in patients with early endometrial cancer or precancerous lesions. In addition, the balloon laserthermia system needs to be modified.

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